REMARKS

I. Status of Claims:

Upon entry of the instant amendment, claims 9-24 will be under examination in this application, claims 1-3 and 7 having been cancelled without prejudice, claims 4-6 and 8 withdrawn from consideration, and claims 9-24 newly added. Support for the claim amendments can be found throughout the application as filed. For example, support for *new claims 9-12* can be found at page 4, lines 6-8; the paragraph bridging pages 6-7; page 8, Example 3; and Figures 2-3; support for *new claims 13-23* can be found at page 6, lines 12-14 and19-23; the paragraph bridging pages 6-7; Examples 3 and 4; and Figures 1-5; and support for *new claim 24* can be found at page 5, lines 28-31; the paragraph bridging pages 5-6; page 6, lines 4-14; and in Figure 1. The language "a DNA encoding the RNA..." that appeared in claim 1 has been revised to the more accurate terminology "a DNA transcribable into the RNA..." in the new claims. No new matter has been added.

II. Objection to the Specification:

The specification is objected to because the nucleotide sequences disclosed at page 9, lines 33-34, are not accompanied by SEQ ID NOs. (*see,* Office Action, page 2, and Notice to Comply).

In response to this objection, Applicants have amended the specification to insert sequence identifiers in the paragraph bridging pages 9-10. A new Sequence Listing is being filed with this Amendment, along with a copy of the Notice to Comply. In view of the foregoing, this objection is believed to have been overcome.

III. Rejection Under 35 U.S.C. § 112, Second Paragraph:

Claim 7 is rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite because claim 7 recites a single stranded RNA comprising a sequence that is not a perfect complement of the single stranded RNA set forth in SEQ ID NO:1 (*see,* Office Action, pages 3-4).

Without acquiescing to this rejection and solely to expedite prosecution, claim 7 has been cancelled. Accordingly, this rejection is moot.

IV. Rejections Under 35 U.S.C. § 102:

(a) Claim 1 is rejected under 35 U.S.C. § 102(a) as allegedly being anticipated by Lopez-Berestein *et al.* (WO 03/061386A1) (*see,* Office Action, page 4).

As a preliminary matter, Applicants note that claim 1 has been canceled. Accordingly, this rejection is moot as to that claim. Applicants address this rejection to the extent that it may be applied to new claim 24.

"A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631 (Fed. Cir. 1987).

New claim 24 requires, in relevant part, that the composition comprises as an active ingredient "a single-stranded RNA that is perfectly complementary to the nucleotide sequence of SEQ ID NO:1." Lopez-Berestein *et al.* does not teach or suggest any single-stranded RNA that is perfectly complementary to the nucleotide sequence of SEQ ID NO:1. It is noted that the Office Action did not reject original claim 2 over Lopez-Berestein *et al.* Original claim 2 recited: "The cell growth-suppressing agent of claim 1, wherein the single-stranded RNA is complementary to the nucleotide sequence of the WT1 gene transcript shown in SEQ ID NO:1." Accordingly, Applicants respectfully submit that there are no grounds for rejecting new claim 24 under 35 U.S.C. § 102(a) over Lopez-Berestein *et al.*

(b) Claim 1 is rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Sugiyama *et al.* (EP 0 841 068 A1) (*see,* Office Action, page 5).

As noted above, claim 1 has been canceled. Accordingly, this rejection is moot as to that claim. Applicants address this rejection to the extent that it may be applied to new claim 24.

New claim 24 recites, in relevant part, that the composition comprises as an active ingredient "a single-stranded RNA that is perfectly complementary to the nucleotide sequence of SEQ ID NO:1." Sugiyama *et al.* does not teach or suggest any single-stranded RNA that is

perfectly complementary to the nucleotide sequence of SEQ ID NO:1. It is also noted that the Office Action did not reject original claim 2 (directed to single-stranded RNA that is complementary to the nucleotide sequence of SEQ ID NO:1) over Sugiyama *et al.* Accordingly, Applicants respectfully submit that there are no grounds for rejecting new claim 24 under 35 U.S.C. § 102(b) over Sugiyama *et al.*

(c) Claim 1 is rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Hübinger *et al.* (*Exp. Hematol.*, 29:1226-1235 (2001)) (*see,* Office Action, page 5).

As noted above, claim 1 has been canceled. Accordingly, this rejection is moot as to that claim. Applicants address this rejection to the extent that it may be applied to new claim 24.

New claim 24 recites, in relevant part, that the composition comprises as an active ingredient "a single-stranded RNA that is perfectly complementary to the nucleotide sequence of SEQ ID NO:1." Hübinger *et al.* does not teach or suggest any single-stranded RNA that is perfectly complementary to the nucleotide sequence of SEQ ID NO:1. Applicants also note that the Office Action did not reject claim 2 over Hübinger *et al.* In view of the foregoing, Applicants respectfully submit that there are no grounds for rejecting new claim 24 under 35 U.S.C. § 102(b) over Hübinger *et al.*

(d) Claim 1 is rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Sugiyama *et al.* (US 6,034,235) (see, Office Action, paragraph bridging pages 5-6).

As noted above, claim 1 has been canceled. Accordingly, this rejection is moot as to that claim. Applicants address this rejection to the extent that it may be applied to new claim 24.

New claim 24 recites, in relevant part, that the composition comprises as an active ingredient "a single-stranded RNA that is perfectly complementary to the nucleotide sequence of SEQ ID NO:1." Sugiyama *et al.* does not teach or suggest any single-stranded RNA that is perfectly complementary to the nucleotide sequence of SEQ ID NO:1. The Office Action did not reject claim 2 over Sugiyama *et al.* purportedly because it recognized that Sugiyama does not teach or suggest a single-stranded RNA that is complementary (let alone perfectly complementary) to the nucleotide sequence of SEQ ID NO:1. Accordingly, Applicants

respectfully submit that there are no grounds for rejecting new claim 24 under 35 U.S.C. § 102(b) over Sugiyama *et al.*

(e) Claims 1, 3, and 7 are rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Mourelatos *et al.* (*Genes & Dev.*, 16:720-728 (2002)) (*see,* Office Action, page 6).

As a preliminary matter, Applicants note that claims 1, 3, and 7 have been cancelled. Thus, this rejection as applied to those claims is moot.

With respect to new claims 9-23, Applicants note that Mourelatos *et al.* fail to teach or suggest any method for suppressing cell growth using a single-stranded RNA that is complementary to the nucleotide sequence of SEQ ID NO:1 (as in claim 9), that comprises the nucleotide sequence of SEQ ID NO:2 (as in claim 13), or that consists of the nucleotide sequence of SEQ ID NO:2 (as in claim 20). Mourelatos is directed to identifying small RNAs that are associated with the Gemin3-Gemin4-eIF2C2 particle. Mourelatos in fact states that "the function of miRNAs is presently unknown. . ." (*see,* page 726, left column, second sentence). Thus, Applicants respectfully submit that claims 9-23 are novel over Mourelatos *et al.*

New claim 24 recites, in relevant part, that the composition comprises as an active ingredient "a single-stranded RNA that is perfectly complementary to the nucleotide sequence of SEQ ID NO:1." Mourelatos *et al.* does not teach or suggest any single-stranded RNA that is perfectly complementary to the nucleotide sequence of SEQ ID NO:1. In recognizing this fact, the Office Action did not reject claim 2 over Mourelatos *et al.* Accordingly, Applicants respectfully submit that claim 24 is also novel over Mourelatos *et al.*

(f) Claims 1, 3, and 7 are rejected under 35 U.S.C. § 102(e) as allegedly being anticipated by Mounts (US 2005/0118625 A1) (*see,* Office Action, page 7).

As claims 1, 3, and 7 have been cancelled, this rejection as applied to those claims is moot.

With respect to new claims 9-23, Applicants note that Mounts fails to teach or suggest any method for suppressing cell growth using a single-stranded RNA that is complementary to the nucleotide sequence of SEQ ID NO:1 (as in claim 9), that comprises the nucleotide sequence

of SEQ ID NO:2 (as in claim 13), or that consists of the nucleotide sequence of SEQ ID NO:2 (as in claim 20). Rather, Mounts is directed to identifying genes that are differentially expressed in osteoarthritis cartilage cells using polynucleotide probes that are stably attached to substrate supports and hybridize under stringent or nucleic acid array hybridization conditions to human protease or osteoarthritis genes (*see,* Abstract and [0006] of Mounts). Thus, Applicants respectfully submit that claims 9-23 are novel over Mounts.

New claim 24 recites, in relevant part, that the cell growth-suppressing agent comprises as an active ingredient "a single-stranded RNA that is perfectly complementary to the nucleotide sequence of SEQ ID NO:1." Mounts does not teach or suggest any single-stranded RNA that is perfectly complementary to the nucleotide sequence of SEQ ID NO:1. In recognizing this fact, the Office Action did not reject claim 2 over Mounts. Accordingly, Applicants respectfully submit that claim 24 is also novel over Mounts.

V. Rejections Under 35 U.S.C. § 103(a):

(a) Claims 1-2 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Sugiyama *et al.* (US 6,225,051) (*see,* Office Action, pages 8-9).

The Office Action acknowledges that Sugiyama *et al.* do not teach a composition comprising a single-stranded RNA that is complementary to the present application's SEQ ID NO:1, wherein the composition has cell-growth suppressing activity; however, the Office Action asserts that the claimed invention would have been obvious. The Office Action reasons that the ordinary artisan would have a reasonable expectation of success of arriving at Applicants' claimed invention, because Sugiyama teaches a DNA sequence (Sugiyama's SEQ ID NO:12) that is complementary to the present SEQ ID NO:1 and hybridizes with WT1 mRNA, and that WT1 expression is associated with cancer growth. The Office Action also alleges that the ordinary artisan would readily recognize that SEQ ID NO:12 of Sugiyama would "hybridize specifically to the cancer cell growth-associated WT1 mRNA by antisense mechanism, thereby functioning as an antisense agent that suppresses cancer cell growth." (*see,* Office Action, page 9, second paragraph). Applicants traverse.

As claims 1 and 2 have been cancelled, this rejection as applied to those claims is moot. Applicants address this rejection with respect to the new claims.

New claim 24 recites, in relevant part, that the composition comprises as an active ingredient "a single-stranded RNA that is perfectly complementary to the nucleotide sequence of SEQ ID NO:1."

The only teaching in Sugiyama *et al.* of any single-stranded sequence that is perfectly complementary to the nucleotide sequence of SEQ ID NO:1 is in Example 3, where Sugiyama discloses SEQ ID NO:12 - a DNA sequence that is complementary to SEQ ID NO:1 of the present application. In that Example, Sugiyama *et al.* teach a method of nested polymerase chain reaction (PCR) to determine the expression level of the WT1 gene in $CD34^-$ fractions isolated from patients to whom granulocyte stimulating factor (G-CSF) had been administered. Sugiyama's method uses SEQ ID NO:12 as an inner antisense DNA primer to perform the second round of a PCR (*see,* Table 3; col. 12, ll. 28-49).

There is no reason derivable from Sugiyama to synthesize an RNA antisense nucleotide molecule of SEQ ID NO:12. Specific hybridization of a DNA primer with a certain partial sequence of a nucleic acid sequence for purposes of PCR does not in any way suggest to the ordinary artisan that that same primer be modified into an RNA, whether for use as a microRNA for suppressing that nucleic acid's expression or for any other purpose. Thus, there is no motivation to make the single-stranded RNA of new claim 24. There is no support in Sugiyama nor in the knowledge of those of ordinary skill in the art for the Office Action's conclusory allegation that the ordinary artisan would readily recognize that SEQ ID NO:12 of Sugiyama would "hybridize specifically to the cancer cell growth-associated WT1 mRNA by antisense mechanism, thereby functioning as an antisense agent that suppresses cancer cell growth." Use of a primer for PCR is for purposes of amplification of a nucleic acid; use of an miRNA is for purposes of decreasing expression of the nucleic acid. That a primer works for amplification is in no way predictive of its use for suppression of nucleic acid expression. At best, Sugiyama teaches that SEQ ID NO:12 can be used as a DNA primer for PCR to measure the expression level of WT1. To extend Sugiyama's teaching to arrive at Applicants' claimed invention would

amount to nothing more than a use of Applicants' specification as a blueprint to piece together the claimed invention.

In view of the foregoing remarks, Applicants respectfully request that there exist no grounds to reject new claim 24 under 35 U.S.C. § 103.

New method claims 9-12 are drawn to methods for suppressing cell growth in a subject in need thereof by administering a composition that includes as an active ingredient any one of: a single-stranded RNA complementary to the nucleotide sequence of SEQ ID NO:1; a DNA transcribable into the RNA of (a); or a vector comprising the DNA of (b). Sugiyama does not teach these claimed methods. Sugiyama teaches the use of WT1 as a marker for solid cancer cells. In addition, it teaches the use of WT1 gene expression in $CD34^-$ cell fractions as a marker of contamination with leukemia cells and solid cancer cells. Sugiyama's reverse PCR DNA primer having SEQ ID NO:12 (listed in Table 3 at col. 12) - a DNA sequence that is complementary to SEQ ID NO:1 of the present application - was in fact used to determine the expression level of WT1 in $CD34^-$ cell fractions. There is simply no motivation in Sugiyama for using SEQ ID NO:12 (whether as a DNA, an RNA, or any other form) in a method of suppressing cell growth in a subject in need thereof . The only motivation regarding use of that primer is to use it to measure the expression level of WT1. The mere fact that the primer is referred to in Sugiyama as "an antisense primer" does not make the primer one that is capable of functioning as an expression-inhibiting antisense molecule. Read in context, the term "antisense primer" is used in Sugiyama to mean a "reverse primer" and not to attribute any sort of "antisense" activity to SEQ ID NO:12. Accordingly, Applicants respectfully request that there exist no grounds to reject new claim 9-12 under 35 U.S.C. § 103.

With respect to new method claims 13-23, Applicants note that Sugiyama does not teach a single-stranded RNA comprising (or consisting of) the nucleotide sequence of SEQ ID NO:2, nor a DNA transcribable into that RNA, nor a vector comprising such a DNA, and certainly does not teach any method of using such an RNA, DNA or vector. Consistent with this fact, the Office Action did not reject original claim 3 as obvious over Sugiyama. Accordingly, Applicants respectfully submit that claims 13-23 are also nonobvious over Sugiyama.

(b) Claims 1-2 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Ware et al. (US 6,232,073) (*see,* Office Action, pages 9-10).

The Office Action argues that, although Ware *et al.* do not teach a single-stranded RNA complementary to the present application's SEQ ID NO:1, it would have been obvious to one of ordinary skill in the art to synthesize an antisense RNA corresponding to the antisense DNA primer having a sequence set forth in SEQ ID NO:30 of Ware and to use that antisense RNA as a cell growth-suppressing agent. The Action reasoned that the claimed invention would have been *prima facie* obvious "[s]ince a WT1 mRNA-specific antisense nucleotide sequence was already disclosed by Ware et al., one of ordinary skill in the art would have readily recognized that the RNA sequence of the WT1 mRNA-specific antisense nucleotide sequence, SEQ ID NO:30, of Ware et al. would also hybridize specifically to the cancer cell growth-associated WT1 mRNA by antisense mechanism, thereby suppressing cancer cell growth." (*see,* Office Action, page 10, second full paragraph). Applicants traverse.

As claims 1 and 2 have been cancelled, this rejection as applied to those claims is moot. This rejection is considered in the context of the new claims.

New claim 24 recites, in relevant part, that the composition comprises as an active ingredient "a single-stranded RNA that is perfectly complementary to the nucleotide sequence of SEQ ID NO:1."

Ware *et al.* teach that the presence of a shortened WT1 transcript is an indicator for detecting cancer in a subject. In Example 2, Ware makes use of several different PCR primer pairs to test for this shortened transcript. One of these pairs includes as the antisense primer SEQ ID NO:30 - a DNA sequence that is complementary to SEQ ID NO:1 of the present application (*see,* Table 1, col. 12, "Antisense," No. 13).

There is simply no reason provided in Ware to synthesize an RNA antisense nucleotide molecule of SEQ ID NO:30. Specific hybridization of a DNA primer with a certain partial sequence of a nucleic acid for purposes of PCR does not in any way suggest to the ordinary artisan that that same primer be produced as an RNA, whether for use as a microRNA for suppressing that nucleic acid's expression or for any other purpose. Thus, there is no motivation to make the single-stranded RNA of new claim 24. There is simply no support for the Office

Action's conclusory allegation that the ordinary artisan "would have readily recognized that the RNA sequence of the WT1 mRNA-specific antisense nucleotide sequence, SEQ ID NO:30, of Ware et al. would also hybridize specifically to the cancer cell growth-associated WT1 mRNA by antisense mechanism, thereby suppressing cancer cell growth." Use of a DNA primer for PCR is for purposes of amplification of a nucleic acid; use of an miRNA is for purposes of decreasing expression of the nucleic acid. That a DNA primer works for amplification is in no way predictive of its corresponding RNA's use for suppression of nucleic acid expression. It is important to note that SEQ ID NO:30 is called "antisense" in the sense that it is a "reverse" primer – *i.e.,* a 3' primer. Ware does not teach or suggest the use of SEQ ID NO:30 as a molecule having "antisense activity" – i.e., activity suppressing nucleic acid expression. It is not at all obvious that any given DNA primer that is "antisense" to a sequence will work to suppress expression. At best, Ware teaches that a DNA with SEQ ID NO:30 can be used as a DNA primer for PCR to measure the expression level of a truncated WT1 transcript. To extend Ware's teaching to arrive at Applicants' claimed invention is nothing more than a use of Applicants' specification as a blueprint to piece together the claimed invention.

In view of the foregoing remarks, Applicants respectfully request that this rejection under 35 U.S.C. § 103 be reconsidered and withdrawn.

New method claims 9-12 are drawn to methods for suppressing cell growth in a subject in need thereof by administering a composition that includes as an active ingredient any one of: a single-stranded RNA complementary to the nucleotide sequence of SEQ ID NO:1; a DNA transcribable into the RNA of (a); or a vector comprising the DNA of (b). Ware does not teach these claimed methods. Ware teaches the detection of a truncated WT1 transcript as a marker for detecting cancer in a subject. SEQ ID NO:30 of Ware (col. 12, No. 13) was used, among others, in a new test for detecting neoplastic tissue. Ware does not teach any methods of using SEQ ID NO:30 as DNA, RNA, or any other form for suppressing cell growth in a subject in need thereof. The use of a 3' RT-PCR primer for amplification provides no motivation to use that primer in a method for suppressing cell growth. In view of the foregoing, Applicants respectfully submit that claims 9-12 are nonobvious over Ware.

With respect to new method claims 13-23, Applicants note that Ware does not teach a single-stranded RNA comprising (or consisting of) the nucleotide sequence of SEQ ID NO:2, nor a DNA transcribable into that RNA, nor a vector comprising such a DNA, and certainly does not teach any method of using such an RNA, DNA or vector. Consistent with this fact, the Office Action did not reject the original claim 3 as obvious over Ware. In view of the foregoing, Applicants respectfully submit that claims 13-23 are also nonobvious over Ware.

VI. Rejections Under Doctrine of Obviousness-Type Double Patenting:

Claim 1 is rejected for nonstatutory obviousness-type double patenting as purportedly being unpatentable over claim 1 of US 6,034,235 (*see,* Office Action, pages 11-12).

Claim 1 has been canceled herein. Accordingly, this rejection is moot. However, Applicants address this rejection with respect to new claim 24.

A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim because the examined application claim is either anticipated by, or would have been obvious over, the reference claim. *See*, *In re Berg*, 140 F.3d 1428 (Fed. Cir. 1998).

New claim 24 of the present application recites: "A composition comprising, as an active ingredient, a single-stranded RNA that is perfectly complementary to the nucleotide sequence of SEQ ID NO:1, wherein the composition has cell growth suppressing activity."

Claim 1 of U.S. Patent No. 6,034,235 recites: "A growth inhibitor for leukemia cells comprising an antisense oligonucleotide to the Wilm's tumor gene wherein said oligonucleotide is 9-30 nucleotides in length comprising all or a portion of SEQ ID NOS: 2, 4, 6, or 8 and a pharmaceutically acceptable carrier."

Applicants note that this rejection was applied, in part, because previously pending claim 1 recited, in relevant part, "a single-stranded RNA complementary to a transcript of WT1" without specifying the degree of complementarity. New claim 24 specifically requires that the single-stranded RNA be perfectly complementary to the nucleotide sequence of SEQ ID NO:1. U.S. Patent No. 6,034,235 does not teach any sequence that is perfectly complementary to the

nucleotide sequence of SEQ ID NO:1. Recognizing this fact, the Office Action did not reject original claim 2 under nonstatutory obviousness-type double patenting over claim 1 of U.S. Patent No. 6,034,235. Accordingly, Applicants respectfully aver that the grounds for this rejection have been overcome.

CONCLUSION

Applicants respectfully request withdrawal of all outstanding rejections and allowance of the claims.

Other than the three-month extension fee and the IDS filing fee, no additional fees are believed to due with this filing. If Applicants are mistaken, please apply any required charges or credits to Deposit Account No. 06-1050, referencing Attorney Docket No. 14875-0169US1.

Respectfully submitted,

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